Answer 1:

Bibliographic Information

Encapsulation of the transition metal compounds carboplatin (CP) and lobaplatin (LP) in different types of liposomes and their physicochemical, biochemical and biological characterization. Reszka, Regina; Fichtner, Iduna; Goan, Silvia-Renate; Rudolph, Michael; Winter, Roland. Max-Delbruck-Centrum fur Molekulare Medizin, Berlin, Germany. Editor(s): Trautwein, Alfred X. Bioinorganic Chemistry (1997), 145-166. Publisher: Wiley-VCH Verlag GmbH, Weinheim, Germany CODEN: 65TRAJ Conference written in English. CAN 128:248493 AN 1998:231297 CAPLUS

Abstract

The dose limiting factor in the treatment of head and neck as well as ovarian cancer with carboplatin and more recently lobaplatin is the myelotoxicity of both substances. In contrast, a stimulation of hematopoiesis was obsd. when these anticancer agents were applied to mice or rats in a specific liposomally encapsulated form. The mechanism of this hematopoietic stimulation, the therapeutic efficacy and the alteration of the pharmacokinetic behavior were investigated with respect to the lipid compn., the prepn. technique, the size of the liposomes, and the interaction between the platinum compds. and the liposomal components. In vitro expts. were carried out to investigate the role of peritoneal macrophages in the decompn. of encapsulated carboplatin and the stimulation of cytokine release as a possible main step for the activation of the hematopoietic system. During the biophys. studies, we were not able to detect a significant perturbation or intermol. interactions of carboplatin or lobaplatin with the lipid system (1,2 Dipalmitoyl-sn-glycero-3-phosphocholine, DPPC). The in vitro treatment of peritoneal macrophages (mice) with carboplatin or lobaplatin encapsulated in reverse phase evapn. vesicles (REV, HEPC:CH, molar ratio 1:0.25 or 1:0.1, size distribution 0.2 to 1.5 μm) showed a stimulation of cytokines measured for instance as TNF-release. In parallel no decompn. products of carboplatin could be detected by HPLC. Following a single (i.v. or i.p.) injection, carboplatin liposomes (CPL) induced a five- or tenfold, at least 4 mo lasting increase in peripheral white blood cells compared to the free drug in mice. A second administration in a 7-10 wk distance was able to a repeated stimulation. The colony forming activity and the percentage of cells in S-phase were elevated in spleen three days after treatment of mice with CPL, while these parameters remained unchanged in the bone marrow.

Serum taken from CPL-treated nude or normal mice induced a significant colony formation of bone marrow cells in a soft agar culture. In the syngeneic ascitic murine P388 leukemia and the MethA sarcoma liposomal encapsulation resulted in a loss of antitumor activity. On contrary, in 3/6 solidly growing breast carcinomas, xenografted to nude mice, CPL had a superior tumor inhibiting effect compared to free carboplatin, which could be further improved by using the combination of free and liposomal drug. A combination of CPL with either cyclophosphamide or free carboplatin increased the antitumor activity and prevented the cytostatic-induced leukopenia. As mechanism for this unexpected pharmacol. behavior of liposomal carboplatin, we suggested, that the vesicles are taken up by the monocyte/macrophage system as their natural target. Within these cells CPL are metabolized and induce the prodn. and release of cytokines which, secondarily, stimulate hematopoiesis. Pharmacokinetic data and measurements of cytokine levels in serum of treated mice support this hypothesis. Free carboplatin, empty liposomes or cisplatin-liposomes never caused a similar pharmacol. behavior. Lobaplatin encapsulated in REV (HEPC:CH, molar ratio 1:0.1, size distribution 0.2 to 1.5 μm) will be tested further on in vivo. First preliminary observations suggest that LPL can also stimulate the hematopoietic system.